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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,012	01/22/2001	Michael J. McCluskie	C1040/7010	9273

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 08/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/768,012	Applicant(s) MCCLUSKIE ET AL.	
	Examiner Dave Nguyen	Art Unit 1632	

-- Th MAILING DATE of this communication appears on th cov r she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,52,55,78,112,124,135,136,142,150 and 152* is/are pending in the application.

4a) Of the above claim(s) *78,112,124,135,136,142,150 and 152* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,52,55 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,10,,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Claim 1 has been amended by the response filed March 29, 2001.

Applicants in the Response filed March 22, 2002 elected Invention of Group 1, claims 1-31, 52, 100, mucosal administration with mouth as the targeted delivery site, a Th1 adjuvant that is QS21, a Th2 adjuvant that is a mucosal adjuvant (bacterial toxin), the species of a liquid solution as a formulation, the species of oral administration route, the species of mucosal immune response, the species of anti-viral agent as a therapeutic agent, and the species of a viral antigen without traverse. However, the species restriction has been withdrawn by the examiner since there is no prior art of record that teaches, suggests, or provides a motivation to employ a non-CpG Th2 immunostimulatory nucleic which can not have any CG dinucleotides, a poly T motif (TTTT), and/or a poly G motif (GGGG), and it must induce a Th2 response when administered mucosally or parenerally.

Claims 78, 112, 124, , 135, 136, 142, 150, 152 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31, 52, 100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of employing Th2 immunostimulatory nucleic acid of at least 8 nucleotides and comprising 5' TCCA 3' as a Th2 adjuvant in combination with an antigen for mucosal administration to a vertebrate, does not reasonably provide enablement for any other claimed embodiment. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims embraces an a mucosal or oral delivery method of employing any nucleic acid which can not have any CG dinucleotides, a poly T motif (TTTT), and/or a poly G motif (GGGG) to induce an immune response to an antigen in any and/or all subjects including reptiles, birds, amphibians, mammals and humans.

The application provides a rather unexpected result, which demonstrates that mucosal or parenteral administration of a hepatitis surface antigen and the Th2 immunostimulatory nucleic acid of SEQ ID NO: 1 or 2 induces a Th2 response (augmenting IgG1) in mice. The state of the prior art prior to filing date of this as-filed application focuses mainly on the use of vectors that intrinsically contain CpG dinucleotides as expression vectors, of palindromic oligos to treat tumors, or of unmethylated CpG containing oligos and/or plasmids as Th1 adjuvants. The issue is then whether or not a skilled artisan on the basis of applicant's disclosure would have reasonably be able to extrapolate the rather unexpected results as demonstrated by the as-filed specification to the full breadth of the claim. The state of the prior art exemplified by Yamamoto (Antisense Research and Development 4:119-122, 1994) *et al.* teaches that the use of a specific palindromic sequence and some molecular size of synthetic oligoDNA is required to induce the biological activity. Messina *et al.* (Cellular Immunology 147, 148-157, 1993) state that "at present, the mechanism by which DNA triggers proliferation is not known. Since only certain natural as well as synthetic DNA are active, it appears that mitogenicity results from an interaction with high ligand specificity rather than simple binding of DNA to cells on the basis of charges". Branda *et al.* (J. of Laboratory and Clinical Medicine, 128, 3, pp. 329-38, 1996) state that

"inspection of the oligodeoxynucleotides known to enhance B cell function (Table I) fails to show any important homologies", and that "examination of Table I indicates that some oligomers that stimulate B cells do not have the CpG motif (see reference 16), whereas others that contain CpG dinucleotides do not activate lymphocytes (see references 22, 23, 24, and 26)" (page 336, column 2). In addition, Table I of Branda *et al.* further indicates that oligonucleotides exhibit no immune-neutralizing and/or immune-inhibitory effects (items 10 and 13, for example). The as filed specification (page 66) and McCluskie et al. (Vaccine, 19, pp. 413-422, 2001) teaches that "the stimulatory effects of non-CpG ODN (containing 5' TCCA 3' and has more than 8 nucleotide residues) were totally unexpected since non-CpG ODN do not have such an effect when delivered by a parenteral route (e.g., IM injection)" (page 420, column 2).

In addition, McCluskie *et al.* (Vaccine 19, pp. 2657-02660, 2001) teaches on page 2660, column 1:

> In this study, we have shown that both CpG and non-CpG ODN have immunostimulatory properties. This does not appear to be due solely to the phosphorothioate backbone, as we have previously suggested, but rather a sequence-related effect, since phosphorothioate poly_T and poly-GC ODN of similar size do not have such an immunostimulatory effect.

McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) teaches (p. 4465, column 1):

> Results were due to the CpG motif rather than to a nonspecific effect of the ODN backbone, since mice immunized with 1 ug of HbsAg plus 10 ug of non-CpG ODNs had no (7 out of 10) or verlow (3 of 10) titers of anti-HBs IgG Abs.

McCluskie *et al.* (The J. of Immunology, 161, pp. 4463-4466, 1998) also teaches (page 4465, column 1, third paragraph) that "no IgA was detected in the lung washes with 1-ug dose of non-CpG ODN/CT" .

Thus, given that the precise common structure by which a non-CpG DNA mediates either an immune-stimulatory effect so as to generate a therapeutic effect in the treatment of any immune related disease or disorder is not completely understood, and that the exemplified results were rather unexpected due to specific non-CpG ODN and musosal routes being used, and given the complexities of Th2 responses associated with nucleic acids and/or routes of administration, it is not apparent as to how one skilled in the art, without undue experimentation, as to how to identify a common mechanism or structural feature which is found in a contemplated and claimed Th2 immunostimulatory DNA sequences other than the exemplified ones, which must exhibit the claimed property.

Furthermore and more specifically as to methods claimed wherein any Th2 immunostimulatory DNA is employed as an orally immunogenic composition, and to further support the non-correlation between a murine model subjected to an oral DNA vaccine and a human subject (as specifically claimed in dependent claims of the currently pending claims), the state of the art exemplified by McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen"

(page 297, column 1).

Thus, it is not apparent as to how one skilled in the art reasonably extrapolates, without undue experimentation, from the disclosure of the application to the full breadth of the claims, given the protocols and data provided by the as-filed specification and the art of record, wherein an immunogenic composition which is only required to contain Th2 immunostimulatory DNA for use as an immunogenic composition by any mucosal route and parenteral route, particularly given the reasons set forth above.

Note that it is not apparent as to how the mouse model using one single species of immunostimulatory nucleic acid of more than 8 nucleotides and containing the 5' TCCA 3' motif is reasonably extrapolated to the full scope of the claimed invention, particularly given that there is no evidence that the mice model and/or the Th2 activity of the exemplified ODN and/or the mucosal routes employed in the working examples are a general phenomenon for the make and use of any other Th2 immunostimulatory DNA and any routes of administration other than mucosal routes in any and/or all claimed subjects, and given the doubts expressed in the art of record.

The prior art of record does not teach or suggest the claimed invention as claimed.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER